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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : A61K 31/55

A1

(11) International Publication Number: WO 88/ 07858

(43) International Publication Date: 20 October 1988 (20.10.88)

(21) International Application Number: PCT/US88/01169

(22) International Filing Date: 4 April 1988 (04.04.88)

(31) Priority Application Numbers: 036,403
167,663

(32) Priority Dates: 9 April 1987 (09.04.87)
14 March 1988 (14.03.88)

(33) Priority Country: US

(71) Applicant: SMITHKLINE BECKMAN CORPORATION [US/US]; One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101 (US).

(72) Inventors: BONDINELL, William, Edward ; 1512 Franklin Lane, Wayne, PA 19087 (US). ORMSBEE, Herbert, Stowel, III ; 652 Pugh Road, Wayne, PA 19087 (US).

(74) Agents: HALL, Linda, E. et al.; Corporate Patents & Trademarks N-160, SmithKline Beckman Corporation, P.O. Box 7929, Philadelphia, PA 19101 (US).

(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.

(54) Title: SULFINYL AND SULFONYL SUBSTITUTED 3-BENZAZEPINES

(57) Abstract

Sulfinyl and sulfonyl substituted 3-benzazepine compounds are useful in treating and preventing emesis. Particular compounds of this invention are 7-methyl-sulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine and 8-methoxy-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

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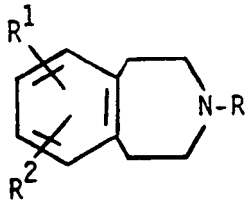
SULFINYL AND SULFONYL SUBSTITUTED 3-BENZAZEPINES

This invention relates to sulfinyl and sulfonyl substituted benzazepine compounds for use in treating emesis.

These compounds are known in the art and may be prepared as shown in European Patent Application 86309846.3. They have been reported as having utility in the treatment of gastrointestinal diseases. It has now been found that the sulfinyl and sulfonyl substituted benzazepine compounds are useful therapeutically for treating or preventing emesis.

According to the present invention there is provided the use of a compound of the formula (I):



(I)

in which:

R is hydrogen, C_1-C_6alkyl or C_3-C_5alkenyl;

R^1 is SOR^3, SO_2R^3 or $SO_2NR^4R^5$;

R^2 is hydrogen, halogen, CF_3, C_1-C_6alkyl or R^6O-;

R^3 is C_1-C_6alkyl or CF_3;

R^4 and R^5 are hydrogen or C_1-C_6alkyl; and

R^6 is hydrogen, C_1-C_6alkyl or C_1-C_6alkanoyl,

provided that when R^1 is SO_2NH_2, R^2 is R^6O-, halogen, CF_3 or C_1-C_6alkyl,

or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a medicament for treating or preventing emesis.

Particular compounds of formula (I) are those in which R^1 is in the 7-position. Further particular compounds of formula (I) are those in which R^1 is in the 7-position and R^2 is in the 8-position.

A group of compounds of formula (I) is that in which R^1 is SO_2R^3 or $SO_2NR^4R^5$, R^2 is hydrogen, alkoxy or hydroxy, R^3 is methyl and R is hydrogen and, in addition, R^1 may be in the 7-position and R^2 may be in the 8-position.

Specific compounds of this invention are:

8-hydroxy-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine;

7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine;

8-hydroxy-7-(N-methylsulfamoyl)-2,3,4,5-tetrahydro-1H-3-benzazepine;

8-methoxy-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine;

6-sulfamoyl-2,3,4,5-tetrahydro-1H-3-benzazepine;

7-sulfamoyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

The compounds of formula (I) form pharmaceutically acceptable acid addition salts with organic or inorganic acids. Examples of these acids are hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, tartaric, citric, maleic, lactic, oxalic, succinic, methanesulfonic, and benzenesulfonic acids. The salts are formed according to methods known to the art. If the product is isolated as an acid addition salt, it may be treated with an inorganic or organic base, such as aqueous sodium hydroxide, sodium carbonate, triethylamine, etc.,

and converted to the corresponding free base. The base can then be treated with an appropriate acid, for example in an aqueous miscible solvent, such as a lower alkanol preferably methanol or ethanol, to give the desired salt.

The effect of the pharmacologically active compounds of this invention on emesis is demonstrated in the following test procedure.

Method for Determination of the Anti-emetic Effect in the Conscious Dog

Compounds are administered orally or parenterally to proven apomorphine-sensitive dogs of either sex. After the appropriate time has elapsed (determined by a peak time study), apomorphine hydrochloride (0.1 mg/kg, s.c.) is administered and the frequency of emesis is observed and recorded for the next forty minutes. Emesis is defined as the actual expulsion of stomach contents.

The control group of dogs, also apomorphine-sensitive, receive the test vehicle and apomorphine hydrochloride (0.1 mg/kg, s.c.) Emesis is recorded as with the test animals.

The mean frequency of emesis for the control and test groups is calculated. A value for each test group is then obtained which expresses the percentage increase or decrease in frequency of emesis relative to controls. An effective dose-50% is calculated. The ED_{50} refers to the dose that decreases emesis induced by apomorphine by 50%.

The pharmacologically active compounds of formula (I) can be administered orally or parenterally. Preferably, these compounds are administered in conventional dosage unit forms prepared by combining an appropriate dose of the compound with standard pharmaceutical carriers. The dosage units will contain the active ingredient in an effective amount selected from about 1 mg. to about 250 mg., preferably 10 mg. to 100 mg.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent can include any time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a trouche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg. to about 1 g. If a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampul or an aqueous or nonaqueous liquid suspension.

The pharmaceutical compositions are prepared by conventional techniques involving procedures such as mixing, granulating and compressing when necessary or variously mixing and dissolving the ingredients as appropriate to the desired composition.

The method of treating and preventing emesis in accordance with this invention comprises administering internally to a subject in need of said treatment an effective amount of a compound of formula (I), in particular, 7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine, 6-sulfamoyl-2,3,4,5-tetrahydro-1H-3-benzazepine, 7-sulfamoyl-2,3,4,5-tetrahydro-1H-3-benzazepine, or 8-methoxy-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine or a pharmaceutically acceptable acid addition salt thereof.

The compound will preferably be administered in a dosage unit form orally or parenterally. Advantageously equal doses will be administered one to four times daily with the daily dosage regimen being from about 1 mg. to about 1000 mg., preferably from 10 mg. to 400 mg.

One skilled in the art will recognize that in determining the amounts of the compound needed to produce the desired pharmacological effect without toxic side effects, the activity of the particular compound as well as the size of the host animal must be considered.

The following examples illustrate the invention but are not to be construed as limiting the scope thereof. Temperatures are in degrees Centigrade unless otherwise stated.

EXAMPLE 1

8-Hydroxy-7-sulfamoyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

A mixture of 3-methoxyphenylacetic acid (47.7 g, 0.287 m), thionyl chloride (50 ml) and N,N-dimethylformamide (6 drops) in toluene (500 ml) was stirred for 16 hours at 25° and concentrated in vacuo to afford 3-methoxyphenylacetyl chloride. The acetyl chloride was dissolved in chloroform (100 ml) and added to a solution of aminoacetaldehyde dimethyl acetal (32.1 g, 0.306 m) and triethylamine (32.4 g, 0.320 m) in chloroform (500 ml) stirred at 5°. The mixture was stirred at 25° for 16 hours, washed with water, 1.5N hydrochloric acid and water, dried with magnesium sulfate and concentrated in vacuo to give N-(2,2-dimethoxyethyl)-3-methoxybenzeneacetamide.

A solution of the benzeneacetamide (70 g, 0.277 m) in acetic acid (180 ml) was added with stirring to concentrated hydrochloric acid (120 ml). The mixture was stirred for 16 hours, diluted with ice/water and filtered. The filter cake was dissolved in methylene chloride which was washed with water, dried with magnesium sulfate and concentrated in vacuo to give 2,3-dihydro-8-methoxy-2-oxo-1H-3-benzazepine.

A mixture of 2,3-dihydro-8-methoxy-2-oxo-1H-3-benzazepine (12 g, 0.063 m) and 10% palladium-on-carbon (1.2 g) in acetic acid (200 ml) was shaken in an atmosphere of hydrogen (60 psi), degassed, filtered and concentrated in vacuo. The residue was dissolved in methylene chloride, washed with water, dried with magnesium sulfate and concentrated in vacuo. The residue was triturated with ether and filtered to give 8-methoxy-2-oxo-2,3,4,5-tetrahydro-1H-3-benzazepine.

A suspension of 8-methoxy-2-oxo-2,3,4,5-tetrahydro-1H-3-benzazepine (20.4 g, 0.105 m) in tetrahydrofuran (500 ml) was added to 1M borane in tetrahydrofuran (300 ml) stirred at 5°. The mixture was heated to reflux for 2 hours, cooled, treated with 3N hydrochloric acid (300 ml), concentrated in vacuo to remove tetrahydrofuran and heated to reflux for 1 hour. The mixture was concentrated in vacuo, filtered and the filter cake was dissolved in methanol, heated to reflux, dried with magnesium sulfate and concentrated in vacuo to afford 7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride, m.p. 229-231°.

A mixture of 7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (4.3 g, 0.02 m) and sodium acetate (3.3 g, 0.04 m) in acetic anhydride (13 ml) was refluxed and stirred for 16 hours, concentrated in vacuo and partitioned between methylene chloride and water. The organic phase was dried with magnesium sulfate, filtered and concentrated in vacuo to give 3-acetyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. 89-90°.

3-Acetyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (2.3 g, 0.01 m) was added to chlorosulfonic acid (6 ml) which was stirred at 0°; the mixture was allowed to warm to 25° and stirred for 16 hours. The reaction was carefully poured into ice water and extracted with methylene chloride. The methylene chloride extracts were combined, washed, dried with magnesium sulfate and concentrated in vacuo to give 3-acetyl-7-chlorosulfonyl-8-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. 153-160°.

3-Acetyl-7-chlorosulfonyl-8-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (3 g, 0.007 m) was treated with concentrated ammonium hydroxide (10 ml), stirred for 2 hours and filtered to give 3-acetyl-8-methoxy-7-sulfamoyl-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. 260-263°.

The sulfonamide (2.3 g, 0.007 m) was suspended in 3N hydrochloric acid and heated to reflux for 16 hours. The mixture was concentrated in vacuo and the residue crystallized from methanol to give 8-methoxy-7-sulfamoyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride, m.p. 270-274°.

8-Methoxy-7-sulfamoyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (1.5 g, 0.005 m) was dissolved in 48% hydrobromic acid (15 ml), refluxed for 2 hours and concentrated in vacuo. The residue was triturated with acetone and then recrystallized from methanol to give 8-hydroxy-7-sulfamoyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide, m.p. 315-320° (decomp.).

EXAMPLE 2

8-Hydroxy-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

Method A

3-Acetyl-7-chlorosulfonyl-8-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (18 g, 0.056 m) was added in portions to a mixture of sodium sulfite (8.8 g, 0.069 m) and sodium bicarbonate (10.8 g, 0.115 m) in water (36 ml) stirred at 70°C. There was a vigorous evolution of gas after each addition. The mixture was stirred for fifteen minutes, treated with iodomethane (8.5 ml, 0.136 m) and refluxed for forty-five minutes. The mixture was partitioned between methylene chloride and water. The methylene chloride phase was washed with water, dried with sodium sulfate and concentrated in vacuo to give 3-acetyl-8-methoxy-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. 159-162°C.

Method B

3-Acetyl-7-chlorosulfonyl-8-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (4 g, 0.013 m) was dissolved in glacial acetic acid (80 ml), treated with stannous chloride dihydrate (11.6 g, 0.05 m) and concentrated hydrochloric acid (16 ml) and stirred at 75° for 1 hour. The mixture was cooled, poured into ice water and extracted with ethyl acetate. The combined ethyl acetate extract was washed, dried with magnesium sulfate and concentrated in vacuo to give a mixture of 3-acetyl-7-mercapto-8-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine and the corresponding disulfide.

The crude mixture (3 g) was dissolved in ethanol and treated with sodium borohydride (2 g, 0.05 m) to effect reduction of the disulfide to the mercaptan. Methyl iodide (2 g, 0.014 m) was added and the reaction mixture was stirred at 25° for 1 hour. The mixture was concentrated, partitioned between water and methylene chloride and the combined methylene chloride extract was washed, dried with magnesium sulfate and concentrated in vacuo to give 3-acetyl-8-methoxy-7-methylthio-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. 138-140°.

3-Acetyl-8-methoxy-7-methylthio-2,3,4,5-tetrahydro-1H-3-benzazepine (1.1 g, 0.004 m) dissolved in methylene chloride (10 ml) was treated with 3-chloroperbenzoic acid (1.4 g, 0.008 m) and stirred for 1 hour. The mixture was extracted with 5% aqueous sodium carbonate, washed with water, dried with magnesium sulfate and concentrated in vacuo to give 3-acetyl-8-methoxy-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. 162-164°.

3-Acetyl-8-methoxy-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine (1 g, 0.003 m), prepared as in Method A or B, in 48% hydrobromic acid (15 ml) was heated to reflux for 16 hours and concentrated in vacuo. The residue was triturated with acetone and recrystallized from methanol-water to give 8-hydroxy-7-methylsulfonyl-

2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide, m.p. 300° (decomp.).

Alternatively, 3-acetyl-8-methoxy-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine was treated with 3N hydrochloric acid to give 8-methoxy-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride, m.p. 228.5-229.5°. Refluxing this compound with 48% hydrobromic acid gave 8-hydroxy-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide.

EXAMPLE 3

7-Methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

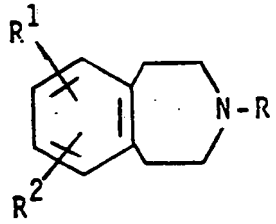
Following the procedure of Examples 1 and 2, 2,3,4,5-tetrahydro-1H-3-benzazepine was converted to 3-acetyl-7-chlorosulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine and then to 3-acetyl-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine which was hydrolyzed with hydrochloric acid to give 7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride, m.p. 275-277°C.

EXAMPLE 4

7-Methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine methanesulfonate (10 mg) is mixed with 75 mg of lactose and 2 mg of magnesium stearate. The resulting mixture is filled into a hard gelatin capsule.

CLAIMS:

1. The use of a compound of the formula:



(I)

in which:

R is hydrogen, C_1-C_6alkyl or C_3-C_5alkenyl;

R^1 is SOR^3, SO_2R^3 or $SO_2NR^4R^5$;

R^2 is hydrogen, halogen, CF_3, C_1-C_6alkyl or R^6O-;

R^3 is C_1-C_6alkyl or trifluoromethyl;

R^4 and R^5 are hydrogen or C_1-C_6alkyl; and

R^6 is hydrogen, C_1-C_6alkyl or C_1-C_6alkanoyl,

provided that when R^1 is SO_2NH_2, R^2 is R^6O-, halogen, CF_3 or C_1-C_6alkyl,

or a pharmaceutically acceptable acid addition salt thereof, in the manufacture of a medicament for treating or preventing emesis.

2. The use of a compound as defined in claim 1 in which R^1 is in the 7-position.

3. The use of a compound as defined in claim 1 in which R^2 is in the 8-position and R^1 is in the 7-position.

4. The use of a compound as defined in claim 1 in which R^1 is SO_2R^3 or $SO_2NR^4R^5$, R^2 is hydrogen or C_1-C_6alkoxy, R^3 is methyl, R is hydrogen, R^2 is in the 8-position and R^1 is in the 7-position.

5. The use of a compound as defined in claim 1 said compound being 7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

6. The use of a compound as defined in claim 1 said compound being 8-methoxy-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US88/01169

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4): A61K 31/55
U.S.Cl.: 514/213

II FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	514/213

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

CAS ON LINE

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	U.S., A, 3,689,649 (DIETRICH) published 05 September 1972. See entire document.	1-13
A	U.S., A, 4,024,128 (KOCH) published 17 May 1977. See entire document.	1-13

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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IV. CERTIFICATION

Date of the Actual Completion of the International Search

28 JULY 1988

Date of Mailing of this International Search Report

25 JUL 1988

International Searching Authority

ISA/US

Signature of Authorized Officer

David B. Springer
DAVID B. SPRINGER